REMARKS

Claims 1-16 are currently pending in the application. Claim 9 is withdrawn. Claims 1, 8, and 12 are amended. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

The specification has been amended to delete the Abstract on page 976. The Abstract on page 201 is the correct Abstract.

Claim Objections

The Office Action states that claims 1-8 and 10-16 are objected to on the grounds that the recitation, "a second amino acid sequence comprising a ligand for a cell surface polypeptide of a leukocyte," is awkwardly presented. The Office Action suggests amendment to, "a second amino acid sequence comprising the amino acid sequence of a ligand for a cell surface polypeptide of a leukocyte."

The claim is intended to limit the second amino acid sequence to being capable of binding to the recited cell surface polypeptide (whether or not the entire second amino acid sequence is required for such binding). Applicants are uncertain as to how the proposed amendment renders the claim language less awkward. Applicants respectfully request further explanation from Examiner regarding this language. Pending such explanation and/or discussion, Applicants respectfully maintain the language as originally entered.

The Office Action states that claim 12 is objected to under 37 CFR 1.75(c) on the grounds that it is of improper dependent form as entered, depending on claim 11. The dependence of claim 12 on claim 11 is the result of a typographical error; claim 12 was intended to depend on claim 1. Applicants thank Examiner for calling their attention to this error and correct it by amending claim 12 to depend from claim 1.

Rejection of Claims 1-8, and 10-16 Under 35 U.S.C. §112, Second Paragraph

The Office Action states that claims 1-8 and 10-16 are rejected for indefiniteness under 35 U.S.C. §112, second paragraph. The Office Action states that the word "some" renders the

claims indefinite. Applicants traverse the rejection, since they submit that the claims clearly read on compositions in which any amount of the recited fusion polypeptide is not bound to the recited cell or virus. In the interest of expediting prosecution, though, Applicants are herewith amending the cited claims to remove the phrase "some of".

The Office Action also states that claim 8 is rejected on the grounds that the recitation "at least about", particularly the word "about", renders the claim indefinite. Applicants respectfully disagree. Nevertheless, in order to expedite prosecution, Applicants are herewith amending claim 8 to remove the word "about".

The Office Action also states that the phrase "modulating an immune response" renders the claims indefinite. Applicants respectfully disagree and traverse the rejection. In fact, the specification describes precisely and in detail what it means to "modulate an immune response" (see, e.g., paragraphs 0047-0048). Furthermore, the specification teaches a number of quantitative assays for detecting modulation of an immune response, providing further definition to the term (see paragraphs 0496-0531). The claim language is not indefinite, and one of ordinary skill in the art can easily and conclusively, following the definitions and teaching of the specification, determine whether a method is "modulating an immune response" and, thus, whether the method falls within this claim limitation.

Furthermore, Applicants note that it is well known to those of ordinary skill in the art that different types of immune responses are reciprocally modulated. E.g., a Th1 response and a Th2 response; a suppressor T cell response and a helper T cell response; and antibody responses of different isotypes and subtypes are frequently reciprocally stimulated and suppressed, i.e. modulated in different directions, in a coordinated or even inevitable manner. It is therefore appropriate and not at all indefinite that the claims encompass "modulating an immune response" in its various manifestations.

Accordingly, in view of the above, Applicants respectfully request that the rejections for indefiniteness be withdrawn.

Rejection of Claim 8 Under 35 U.S.C. §112, First Paragraph

The Office Action states that claim 8 is rejected under 35 U.S.C. §112, first paragraph, on the grounds that it fails to comply with the written description requirement. In particular, the Office Action objects to the recited limitation that the second amino acid sequence comprise at least five contiguous amino acids of a naturally occurring GM-CSF. The Office Action states that this limitation is directed at a genus, and further states that Applicants fail to provide adequate written description of the genus by providing sufficient description of a representative number of species. Applicants traverse the rejection.

First, Applicants note that the Office Action states, "... the cytokine is the active component that provides the adjuvant activity. Thus, the claim is drawn encompass [sic] second amino acid sequence having at least five contiguous amino acids of a naturally occurring GM-CSF, and function as an adjuvant." This statement imputes function to the second amino acid sequence that is not a requirement of the invention, i.e. what is claimed. Indeed, Applicants submit that it is the entire multifunctional molecule of the invention that is responsible for any improved and unexpected "adjuvant" effect. The latter point aside, though, the second amino acid sequence is defined in the claim **not** by any self-contained adjuvant activity, but rather by the ability to bind to a cell surface polypeptide of a leukocyte, as recited in independent claim 1. In addition, it is well settled that, although claims are read in light of the specification, limitations from the specification may not be read into the claims, where the claims are not so narrowly drawn. *In re Prater*, 415 F.2d 1393, 1404-05 (CCPA 1969). In the instant case, the rejection stated in the Office Action is based on an improper reading of a functional limitation into the claims. The recited functional limitation relating to the second amino acid sequence is that the second amino acid sequence is able to bind to a cell surface polypeptide or a leukocyte. The arguments in the Office Action regarding written description are, therefore, not proper or relevant, to the extent that they rely on an impermissible reading of a functional limitation (adjuvant activity) into the claim.

The Office Action states that the specification does not provide the complete structure of naturally occurring GM-CSF. In fact, the specification provides references that teach the full amino acid sequence of GM-CSF (see paragraph 0155).

Furthermore, the specification teaches that the second amino acid sequence preferably includes at least five contiguous amino acids of a cytokine (see paragraph 0008), and more specifically teaches the preferred embodiment wherein the second amino acid sequence comprises at least five contiguous amino acids of naturally occurring GM-CSF (see paragraph 0051).

The Office Action acknowledges that adequate written description can rest on disclosure of relevant identifying characteristics, and sets forth a number of specific means by which this approach can be perfected. For example, the Office Action states that written description can be satisfied by delineation of physical and/or chemical properties and functional characteristics. Applicants agree that such criteria can fulfill the written description requirement. In fact, there is a key functional and physical/chemical limitation in the claims that derives from the description in the specification. That is, that the second amino acid sequence must be a ligand for a cell surface polypeptide of a leukocyte. Applicants further note that there is extensive and well-known information in the literature regarding which amino acids of GM-CSF molecules are necessary and which are not necessary for receptor binding and/or bioactivity. See, for example, Shanafelt et al., 1991, J. Biol. Chem. 266: 13804; Shanafelt and Kastelein, 1989, PNAS 86: 4872; Hercus et al., 1994, Blood 83:3500; Altman and Kastelein, 1995, J. Biol. Chem. 270: 2233; Monfardini et al., 1996, J. Biol. Chem. 271: 2966; Lopez et al., 1992 EMBO 11: 909; Meropol et al., 1992 J. Biol. Chem. 267: 14266; Schanafelt and Kastelein, 1992 J. Biol. Chem., 267: 25466; Seelig et al., 1994, J. Biol. Chem. 269: 5548; Shanafelt et al., 1991, EMBO 10: 4105 (Exhibits A-J, respectively). Thus, one of ordinary skill in the art would easily discern many members of a genus from the disclosures of the instant specification, and would recognize that the inventors were, correspondingly, in possession of many such members.

The Office Action further states that, under the written description requirement, "The full compound is required," citing *Fiers v. Revel* and *Amgen v. Chugai*. The cited cases, however,

dealt with subject matter and issues that are fundamentally different from those of the instant invention. Specifically, the claims at issue in both cited cases were aimed at DNA molecules, the sequences of which were entirely unknown to man and which were not disclosed in the relevant specifications. In both cases, the DNA molecules themselves were claimed on the basis of encoding a given, complete polypeptide (human fibroblast beta interferon and human erythropoietin, respectively), even though the sequences of any such DNA's were not taught in the specifications and were unpublished by anyone at the time of filing. In other words, the DNA molecules were claimed in the absence of knowledge regarding their own, actual physical or chemical identities or properties.

The subject matter now at issue, i.e. the amino acid sequence comprising at least five contiguous amino acid molecules of naturally occurring GM-CSF, differs in at least two important ways from that of *Fiers* and *Amgen*. First, the amino acid sequences of GM-CSF are well-known in the art and are, indeed, provided by the instant specification. Second, the invention, i.e. what is claimed, is further defined by the fact that the "second amino acid sequence" can bind to a cell surface polypeptide of a leukocyte. Thus, unlike the claims of *Fiers* and *Amgen*, the instant claims define the metes and bounds of the claim element by its own structural and physical/chemical properties.

In addition, Applicants note that they were in full possession of the claimed invention at the time the application was filed. The species described fully embody all elements of the invention as claimed, and the specification therefore clearly conveys possession of the claimed invention to one skilled in the art. Applicants further note that the limitation regarding "at least five contiguous amino acids" is meant to exclude compositions failing to meet this standard, and that anyone reasonably skilled in the art could easily discern whether, on that basis, a given method fell within or without the potential purview of the claims in this regard.

Accordingly, Applicants respectfully request that Examiner withdraw the rejections under 35 USC 112, first paragraph.

Rejection of Claims 1-4, 6, 8-10, and 12-16 Under 35 U.S.C. §103

Examiner rejects claims 1-4, 6, 8-10, and 12-16 under 35 U.S.C. §103 as being obvious over Burbage et al. in view of Galili et al. Applicants traverse the rejection.

The Office Action states the following: 1) That the first amino acid sequence used by Burbage et al is ricin; 2) that this amino acid sequence is a lectin; and 3) that this amino acid sequence thus comprises a cell surface binding moiety.

These statements do not accurately reflect the teachings of Burbage et al. First, Burbage et al. teaches that their "first task" was to modify the ricin molecule by making three changes in its amino acid sequence, yielding a molecule that was no longer ricin (page 682, first full paragraph). Their goal in doing so was "to eliminate the normal tissue binding sites on [ricin]", i.e. the galactose binding sites that make ricin a lectin. They characterize the resultant molecule as "lectin-deficient ricin" (abstract and *passim*). Thus, Burbage et al. went to lengths to employ an amino acid sequence that is not a lectin, i.e. does not comprise a cell surface binding moiety. Their goal in doing so was to ensure that the second amino acid sequence, i.e. GM-CSF, was the sole cell surface binding moiety so that it could target the cytoplasmically active toxin moiety ("lectin-deficient ricin") to AML cells, which express the GM-CSF receptor.

Applicants further note that the extensive efforts of Burbage et al. to make ricin "lectin-deficient", and therefore ensure that their molecule lack an essential characteristic of the molecules used in the instant invention, actually teaches away from the instant invention and highlights the non-obviousness of the pending claims.

Galili et al teaches the administration of tumor cells to elicit an antitumor immune response. However, this reference does not teach administration of a multifunctional molecule as is taught in the instant invention.

Therefore, even if the teachings of the references are combined, they do not provide the essential elements of the instant invention.

Furthermore, Burbage et al. teaches its molecule solely as a toxin to eliminate AML cells. Burbage et al. does not teach the ability of the molecule to modulate any immune response when administered in a composition with a cell or a virus. Accordingly, there was no motivation to combine these references and, as set forth above, even if combined they do not lead to the instant invention.

In addition, Examiner rejects claim 5 under 35 U.S.C. §103 as being obvious over Burbage et al. in view of Galili et al., in further view of Meyers et al. Applicants traverse the rejection.

As discussed above, there is no motivation to combine Burbage et al. and Galili et al., and even if combined they do not lead to the instant invention. Their further combination with Meyers et al. does not remedy these deficiencies.

Examiner rejects claims 11 under 35 U.S.C. §103 as being obvious over Burbage et al. in view of Galili et al. Applicants traverse the rejection.

As discussed above, there is no motivation to combine Burbage et al. and Galili et al., and even if combined they do not lead to the instant invention. This deficiency applies equally to the references as applied to claim 11.

Accordingly, in view of the above, Applicants request that all rejections under 35 U.S.C. §103 be withdrawn.

Double Patenting

The Office Action states that the instant claims are rejected under the judicially created doctrine of obviousness type double patenting in view of several co-pending applications. Upon notification of allowable subject matter in the instant case, Applicants will timely file a terminal disclaimer effective to obviate the double patenting rejection.

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with

Applicants' attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

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